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Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy (Review)

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[Intervention Review]

Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy

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ABSTRACT

Background

Recent randomised studies reported that single fraction radiotherapy was as effective as multifraction radiotherapy in relieving pain due to bone metastasis. However, there are concerns about the higher retreatment rates and the efficacy of preventing future complications such as pathological fracture and spinal cord compression by single fraction radiotherapy.

Objectives

To undertake a systematic review and meta-analysis of single fraction radiotherapy versus multifraction radiotherapy for metastatic bone pain relief and prevention of bone complications.

Search methods

Trials were identified through MEDLINE, EMBASE, Cancerlit, reference lists of relevant articles and conference proceedings. Relevant data was extracted.

Selection criteria

Randomised studies comparing single fraction radiotherapy with multifraction radiotherapy on metastatic bone pain

Data collection and analysis

The analyses were performed using intention-to-treat principle. The results were pooled using meta-analysis to estimate the effect of treatment on pain response, re-treatment rate, pathological fracture rate and spinal cord compression rate.

Main results

Eleven trials that involved 3435 patients were identified. Of 3435 patients, 52 patients were randomised more than once for different painful bone metastasis sites. Altogether, 3487 painful sites were randomised. The trials included patients with painful bone metastases of any primary sites, but were mainly prostate, breast and lung. The overall pain response rates for single fraction radiotherapy and multifraction radiotherapy were 60% (1059/1779) and 59% (1038/1769) respectively, giving an odds ratio of 1.03 (95% confidence interval [CI], 0.89 to 1.19) indicating no difference between the two radiotherapy schedules. There was also no difference in complete pain response rates for single fraction radiotherapy (34% [497/1441]) and multifraction radiotherapy (32% [463/1435]) with an odds

ratio of 1.11 (95% CI 0.94 to 1.30). Patients treated by single fraction radiotherapy had a higher re-treatment rate with 21.5% (267/1240) requiring re-treatment compared to 7.4% (91/1236) of patients in the multifraction radiotherapy arm (odds ratio 3.44 [95% CI 2.67 to 4.43]). The pathological fracture rate was also higher in single fraction radiotherapy arm patients. Three percent (37/1240) of patients treated by single fraction radiotherapy developed pathological fracture compared to 1.6% (20/1236) for those treated by multifraction radiotherapy (odds ratio 1.82 [95% CI 1.06 to 3.11]). The spinal cord compression rates were similar for both arms (odds ratio 1.41 [95% CI 0.72 to 2.75]). Repeated analyses excluding dropout patients gave similar results.

Authors' conclusions

Single fraction radiotherapy was as effective as multifraction radiotherapy in relieving metastatic bone pain. However, the retreatment rate and pathological fracture rates were higher after single fraction radiotherapy. Studies with quality of life and health economic end points are warranted to find out the optimal treatment option.

PLAIN LANGUAGE SUMMARY

Easing of bone pain caused by metastatic cancer: single versus multifraction radiotherapy

The spread of tumour to the bone (metastasis) is a common characteristic of many malignancies including cancers of the prostate, breast and lung. This may be associated with pain, compression of the spinal cord and the potential for bone fracture. Radiotherapy is used to treat bone metastases, however, the optimum treatment schedule is unclear. This review compares whether a single fraction of radiotherapy is better than multifractions of radiotherapy for alleviating the symptoms associated with tumours that have spread to the bone. Eleven randomised trials were identified in the published literature that compared single versus multifraction radiotherapy for bone metastases. Pooled analysis of these trials suggested that single fraction radiotherapy was as effective as multifraction radiotherapy in controlling bone pain. However, there were more bone fractures in patients treated by single fraction radiotherapy, and they received further treatment sessions more often than those receiving multifraction radiotherapy.

BACKGROUND

Bone metastasis is a common occurrence in the event of malignancy (Porter 1994) and is the third commonest site of distant metastases after liver and lung (Brown 2001). Although some bone metastases are painless, many frequently cause significant and debilitating pain (Janjan 1998). Besides bone pain, bone metastases can also give rise to pathological fracture (Bunting 2001) and spinal cord compression, which result in significant morbidities. Treatment for bone metastasis often requires a multimodality approach, the main aims of which are to palliate pain and prevent future complications (Bates 1992a).

Radiotherapy is a frequently used modality for bone metastasis and has been shown to be effective in decreasing metastatic bone pain (McQuay 2001) and causing tumour shrinkage or growth inhibition. Radiotherapy is usually given as an outpatient treatment, however, it requires daily hospital attendance, usually at a specialised centre that may be some distance away from patient's home. If the course of radiotherapy is protracted, it may cause considerable problems for the patient, especially those with poor performance status and limited life expectancy. From a health economic point of view, radiotherapy for bone pain constitutes a significant workload of a radiotherapy centre (Crellin 1989). It is, therefore, important to strike a balance between the treatment efficacy, patient convenience and cost (Macklis 1998; Lievens Y 2000).

There is yet no consensus regarding the most appropriate way of delivering radiotherapy for metastatic bone pain (Bates 1992b; Rose 1998; Hoskin 2001b; Chander 1999). The practice differs significantly among different countries (Maher 1992; Lievens 2000) and,indeed, between different treatment centres within the same country (Crellin 1989; Priestman 1989; Ben-Josef 1998; Lawton 1991; Duncan 1993; Stevens 1995; Chow 2000; Roos 2000a). One of the controversies, is whether single fraction radiotherapy is as effective as multifraction radiotherapy. Single fraction radiotherapy is more convenient for the patient and it is also less costly compared to multifraction radiotherapy. However, there are some important concerns relating to single fraction radiotherapy. The equivalent biological dose of single fraction treatment is usually smaller compared to multifraction treatment. As a result, the pain response may be inferior to multifraction radiotherapy

(Ben-Josef 1999; Ratanatharathorn 1999). Even if the initial pain response is similar, it may not be durable enough to ensure that the patient remains asymptomatic. In addition, with a potentially reduced tumoricidal effect, single fraction radiotherapy may not be as effective in preventing complications, such as pathological fracture (Koswig 1999) and spinal cord compression.

OBJECTIVES

Although there are a number of published studies comparing single fraction treatment to multifraction treatment, consensus is still lacking. The purpose of this systematic review is to assess the efficacy of single fraction radiotherapy against multifraction radiotherapy in relieving metastatic bone pain and preventing pathological fracture and spinal cord compression.

METHODS

Criteria for considering studies for this review

Types of studies

Published randomized, controlled trials. Published abstracts were included but unpublished studies were not sought. Studies published in any language were also eligible if they fulfilled the inclusion criteria. No authors were contacted for clarification or verification of patient data.

Types of participants

Patients with painful bone metastases from any primary tumour

Types of interventions

Single fraction external radiotherapy versus multifraction external radiotherapy. Studies of pain relief comparing radioisotopes or drugs were excluded.

Types of outcome measures

The studies included must have at least one pain outcome assessment. All types of pain outcome assessment were allowed. Other outcome measures include the retreatment rate and frequency of pathological fracture and spinal cord compression. The pain response criteria follow the definition of the individual study. In general, complete pain response was defined as no pain and any pain relief was defined as lesser degree of pain compared to the pre-treatment level. However, there are variations among different studies regarding the pain assessment tool, timing in assessing the pain response and whether use of analgesic was used as part of criteria in pain evaluation. The different criteria are summarised in the table of characteristics of included studies.

Search methods for identification of studies

An electronic search of several major medical and scientific databases was undertaken and include the following with dates: Medline (1966 to November 2001), Embase (1980 to November, 2001), CancerLit (1975 to October 2001) and the Controlled Trials Register on the Cochrane Library. The exact search strategy* used was shown as below:

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. Randomized controlled trials/
4. Random allocation/
5. Double blind method/
6. Single blind method/
7. clinical trial.pt.
8. exp Clinical trials/
9. (clin$ adj25 trial$).tw.
10. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).tw.
11. Placebos/
12. placebos.tw.
13. random.tw.
14. Research design/
15. Comparative study/
16. exp Evaluation studies/
17. Follow up studies/
18. Prospective studies/
19. (control$ or prospectiv$ or volunteer$).tw.
20. or/1-19
21. limit 20 to animal
22. limit 20 to human
23. 21 and 22
24. 21 not 23
25. 20 not 24
26. exp Bone Neoplasms/
27. Osseous metastasis or Osseous metastases
28. 26 or 27
29. 25 and 28
30. (radiotherapy or irradiation or radiation).mp. [mp=title, abstract, registry number word, mesh subject heading]
31. 29 and 30
32. (pain or "analges*").mp. [mp=title, abstract, registry number word, mesh subject heading]
33. 31 and 32

All the searched abstracts were screened for relevance. Eligible published studies were also identified from reference lists of retrieved paper, textbooks and review articles. A number of conference proceedings were hand searched for meeting abstract. A

number of specific journals were hand searched up to June 2002, including *British Journal of Cancer*, *Journal of the National Cancer Institute*, *European Journal of Cancer*, *Journal of Clinical Oncology*, *The Lancet Oncology*, *Cancer and Journal of Pain and Symptom Management*. The selection of studies for inclusion was carried out independently by WM Sze and M Shelley.
*NB: The main structure of the search strategy was adapted from the generic search strategy for randomised studies designed by librarians at the Hospital Authority of Hong Kong

Data collection and analysis

The following information was extracted from each relevant article:

1. Patient eligibility criteria
2. Number of patients
3. Radiotherapy fractionation - dose per fraction and number of fractions
4. Pain assessment tools or methods
5. Pain assessment schedule
6. Proportion of missing data of pain evaluation
7. Efficacy:
    i) Overall pain response
    ii) Complete pain response
    iii) Retreatment rate
    iv) Pathological fracture rate
    v) Spinal cord compression rate

The data analyses were made with Review Manager v4.1 supplied by The Cochrane Collaboration. The statistical methods were detailed in the statistical manual of MetaView Version 4 (Deeks 1999). The odds ratio and 95% confidence interval were calculated for each trial and presented in a Forrest plot.

RESULTS

Description of studies

Thirty-one studies were identified as potential trials for inclusion in this review. All studies evaluated external radiotherapy for control of metastatic bone pain. Twenty were excluded from the analysis. Eleven trials that involved 3435 patients were included. Of 3435 patients, 52 patients in two studies (Gaze 1997; Ozsaran 2001a) were randomised more than once for different painful bone metastasis sites. Altogether, 3487 painful sites were randomised. Nine studies were two-arm studies i.e. single fraction versus multifraction. Two studies (Foro 1998a; Ozsaran 2001a) randomised painful sites into 3 arms: single fraction versus two different multifraction schemes. Radomised painful sites in the single fraction arm of these two three-arm studies were counted twice in the analyses. Therefore, 3548 painful sites were included in the analyses. The commonest primaries were prostate cancer (23.5%), breast cancer (39.3%) and lung cancer (19.9%). The most frequent treatment sites were spine (34%) and pelvis (32%). The radiation dose of the single fraction arm ranged from 8 Gy to 10 Gy. The schedules of the multifraction arm ranged from 5 Gy times 3 fractions (5 Gy x 3) to 3 Gy times 10 fractions (3 Gy x 10). The commonest schedules used were 4 Gy x 5 and 3 Gy x 10. A significant number of patients failed to complete the pain evaluation with dropout rates ranging from 0% to 69%.

Risk of bias in included studies

Each study was evaluated for quality using the scale proposed by Jadad (Jadad 1996). These scores were not used as a weighting factor for the analyses. As blinding is usually not feasible for radiotherapy treatment, the scoring questions for blinding were omitted in the quality evaluation. Thus, the maximum score is 3 instead of 5. The scoring questions are listed as below:
Question 1 (Q1): Is the study randomised? - 1 point for yes
Question 2 (Q2): Is the randomisation procedure reported or appropriate? - 1 point for yes
Question 3 (Q3): Are the reasons for withdrawals and dropouts described? - 1 point for yes
All the included studies were randomised. Only 1 out of 11 studies reported the randomisation procedure. Three studies described the reasons for withdrawals and dropouts. The quality scores of included studies are summarised in the table of characteristics of included study.

Effects of interventions

The pain response criteria employed by the included studies were quite heterogeneous. In this review, the criteria for overall and complete pain response of the original studies was used. If there was more than one time point for pain assessment, the time point at four weeks after treatment or closest to four weeks after treatment was used in the analyses. Despite this, the criteria for pain assessment may differ between studies. There was also significant amount of missing data due to dropouts in pain evaluation. To minimise bias arising from missing data, the primary analyses of this review were performed according to intention-to-treat principle (Lewis 1993); i.e. all patients randomised into the original study were included, regardless of the compliance of the treatment or follow-up schedule. This is in contrast to most of the original studies, which excluded those patients who could not complete the subsequent pain evaluation. Repeated analyses excluding dropout patients were performed to test the robustness of the results.
Overall pain response (Forrest plot: intention-to-treat [ITT] - overall response)

All the studies reported overall pain response as one of the outcomes. Altogether, the analyses included 11 trials and 3548 painful sites. The overall pain response rates were similar for single fraction radiotherapy (1059/1779 = 60%) and multifraction radiotherapy (1038/1769 = 59%). The individual odds ratios ranged from 0.50 to 1.27 with a pooled odds ratio for all of the trials of 1.03 with a 95% confidence interval of 0.89 to 1.19. The test for heterogeneity was not statistically significant with P value of 0.7, which indicates that the pooling of the data was valid. The overall odds ratio suggests that there is no difference between single and multiple fraction radiotherapy in terms of overall pain response.

Complete pain response(Forrest plot: ITT - overall response)

Seven studies (BPTWP 1999; Gaze 1997; Kagei 1990; Koswig 1999; Nielsen 1998; Price 1986; Steenland 1999) reported this outcome representing a total of 2876 patients. The complete pain response rates were 34% (497/1441) and 32% (463/1435) for single fraction radiotherapy and multifraction radiotherapy, respectively. The individual odds ratios varied from 0.82 to 3.00. The test for heterogeneity was not statistically significant (P = 0.81) allowing the results to be pooled. The overall odds ratio was 1.11 (95% CI 0.94 to 1.30) which suggests that there was no difference for complete pain response between the single and multiple fraction schedules.

Retreatment rate (Forrest plot: ITT - retreatment rate)

Five studies (BPTWP 1999; Cole 1989; Nielsen 1998; Price 1986; Steenland 1999) had reported re-treatment data and 2476 patients were included in the analysis. There were more retreatments after single fraction radiotherapy (267/1240 = 21.5%) compared to multifraction radiotherapy (91/1236 = 7.4%). The likelihood of re-treatment was 3.44-fold higher (95% CI 2.67 to 4.43) in single fraction radiotherapy arm patients. Test for heterogeneity was insignificant with P value of 0.18.

Pathological fracture (Forrest plot: ITT - fracture rate)

Five studies (BPTWP 1999; Cole 1989; Nielsen 1998; Price 1986; Steenland 1999) reported data for pathological fracture and included a total of 2476 patients. There were more pathological fractures in single fraction radiotherapy arm patients (37/1240 = 3%) than multifraction radiotherapy arm patients (20/1236 = 1.6%). The p-value (0.03) was marginally significant. The individual odds ratios varied considerably from 0.35 to 3.50, although the test for heterogeneity was not significant (P = 0.31). The overall odds ratio was 1.82 (95% CI 1.06 - 3.11) indicating that the risk of pathological fracture was 1.82 times higher in single fraction radiotherapy arm patients compared to the multiple fraction arm.

Spinal cord compression (Forrest plot: ITT - spinal 1 and spinal 2)

Only three studies (BPTWP 1999; Price 1986; Steenland 1999) reported the spinal cord compression rates. Two thousand, two hundred and six patients were randomised in these three studies. The spinal cord compression rates for all randomised patients were not different: 1.9% (21/1102) for single fraction patients and 1.4% (15/1104) for multifraction patients (P = 0.3) (Fig spinal 1).

Of these 2206 patients, only 739 patients had spinal metastases. Reanalysis using the data of these 739 patients showed a similar trend in that the rates were equivalent (single fraction vs multifraction: 5.6% vs 4%, P = 0.3). Tests for heterogeneity in the analysis were not significant (fig spinal 2). These three studies did not stratify the patients by site of involvement, therefore, the subset analysis was not strictly using data from a randomised study setting.

Repeated analyses of the above end points excluding dropout patients only did not alter the conclusions (Table 1).

Side effects

Ten studies (BPTWP 1999; Cole 1989; Foro 1998a; Gaze 1997; Kagei 1990; Nielsen 1998; Ozsaran 2001a; Price 1986; Steenland 1999) reported side effects of the treatment. The commonest side effects reported were nausea and vomiting and were similar in severity for both treatment arms. Only Foro et al reported that there were more transient increases in pain after single dose treatment, however, quantitative data were not available. The data were summarised in the table of characteristics of the included studies.

DISCUSSION

This review confirms that radiotherapy is very effective in relieving metastatic bone pain. Up to 60% of patients will have some pain relief and about one third of them will have complete pain relief. Although the total patient number included in these randomised studies are large, there are still many unanswered questions. The most important problem is that there is no standard criterion in assessing the pain control. The pain assessment tool, the schedule of pain assessment and the definition of pain relief varied within the included studies. As reported in some of the studies (Kagei 1990; Ozsaran 2001a; Price 1986), the efficacy of pain relief would be different if the time point taken to assess the pain relief varied. Although there was variation in the pain response rates at different time points of assessment, the efficacy of single dose radiotherapy was the same as that of multifraction radiotherapy regardless of which time point was actually used (Price 1986; Kagei 1990). The only exception was the Ozsaran study which showed that assessment of pain relief on day 10 after radiotherapy favoured multifraction radiotherapy. The difference became insignificant on the first- and third-month reassessments. Future studies should follow more consistent pain assessment criteria to facilitate comparison and analysis and recently, guidelines for pain assessment were recommended by an international group which may be helpful for investigators in designing future studies (IBMC 2001; Hoskin 2001a).

There was a significant amount of missing data in the pain assessment with dropout rates ranging from 0% to 69%. Common rea-

sons for missing data were patient death and significant ill health preventing the patients from filling in the assessment form. The dropout patients were usually excluded from the pain response analyses. Therefore, most of the analyses were not using the intention-to-treat principle. This may be reasonable if we assume symptomatic relief is irrelevant after patient's death. Nevertheless, whether symptom relief can be achieved or not when a patient's death is imminent, remains uncertain. This is a potential bias when a large proportion of patients are excluded from analysis.

The retreatment rate is 3.4-fold higher in patients treated by single fraction radiotherapy which will counteract the advantages of single fraction radiotherapy. The reasons for the higher re-treatment rate are multiple. One possibility is that the pain response is less durable resulting in re-treatment in subsequent clinical course. However, in studies (Gaze 1997; Nielsen 1998; Price 1986; BPTWP 1999; Steenland 1999) that analysed the time to pain progression or duration of response, there was no evidence that the time to progression was shorter in single dose radiotherapy arm. Therefore, it is unlikely to be the major contributing cause for the higher re-treatment rate. The other possible reason for the higher re-treatment rate in single dose treatment patients is that many oncologists are not willing to give re-treatment after multifraction radiotherapy unless the patient has significant pain. In the Dutch Bone Metastasis Study (Steenland 1999), the pain score before re-treatment was higher in the multifraction radiotherapy group. The possible explanation may be the concern about the potential radiotherapy toxicities after an initial higher dose treatment. The scenario will be different for single dose treatment when the radiotherapy dose is lower. Thus, it is difficult to ascertain that multifraction radiotherapy, in this respect, is superior.

The pathological fracture rate is higher in the single dose radiotherapy arm. The absolute difference of the rate is only 1.3% (3% vs 1.7%). The number needed to treat is about 77, i.e. about 1 more patient will experience pathological fracture when 77 patients are treated by single dose radiotherapy. Although the difference is small, this is a significant complication that should not be overlooked lightly. Theoretically, the difference may be even higher for those who have a more lytic lesion and for those who have a longer survival.

It should be noted that there is a trend of increasing spinal cord compression rates in all three studies analysed for this outcome. However, the number of events were too small to allow sufficient statistical power to test the difference.

There was minimal data to address quality of life issues which should be included in the reporting in future studies. In addition, scant information was available relating to health economics. In the Dutch Bone Metastasis Study (Steenland 1999), the difference in the cost for the two schedules was about 570 Euros in favour of single dose treatment. Nevertheless, the analysis did not include treatment costs for the higher number of pathological fractures.

AUTHORS' CONCLUSIONS

Implications for practice

In conclusion, radiotherapy is effective in relieving metastatic bone pain. There is no difference in the efficacy between single fraction radiotherapy and multifraction radiotherapy. However, the re-treatment rate and pathological fracture rate are higher after single dose radiotherapy. Multifraction radiotherapy remains one of the alternatives in treating metastatic bone pain. This is especially so for patients with lytic lesions and long life expectancy. More data are needed to find out the optimal treatment strategy.

Implications for research

Although a significant proportion of patients had some pain relief after radiotherapy, complete pain relief was still not achieved in about two-thirds of patients. The incorporation of different modalities like radio-isotopes or medications e.g. bisphosphonates may further improve the pain relief efficacy. Studies testing the optimal use of various modalities are warranted. More refinement of patient selection such as subsets of different life expectancy and various types of pain, will be helpful to address these questions. Future studies should use standardised criteria for pain assessment so that results can be compared. A more robust statistical approach should be applied to minimize the impact of missing data. Quality of life and health economics end points should be incorporated into the study protocol.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

BPTWP 1999

Methods	Randomized controlled trial Quality score (1/0/1) Pain assessment criteria: 4 -point category for pain Response - improvement by at least 1 category within 1 year Complete response - no pain Pain assessment schedule: 2 weeks, 1,2,3,4,5,6,8,10 and 12 months
Participants	Painful bone metastasis Exclusion: pathological # Randomised sites: 383 vs 378 Primary tumours:prostate (34%), breast (36%), lung (12%)
Interventions	8 Gy x 1 vs 4 Gy x 5 or 3Gy x 10
Outcomes	Overall response Complete response Re-treatment Fracture Spinal cord compression
Notes	Missing data in pain assessment:80 / 761 (10.5%) Time point taken for pain response analysis in this review: Within 1 year Side effects: Nausea 56% vs 65% Vomiting 30% vs 32%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Cole 1989

Methods	Randomized controlled trial Quality score (1/0/0) Pain assessment criteria: Five point categorical pain score Response - Best score within 6 months with at least improvement by one category. Pain assessment schedule: Daily chart by patients for 28 days from start of treatment. Monthly assessment by doctor
Participants	Painful bone metastasis. Neurologic compression, established or impending pathological # excluded Randomised sites: 16 vs 13 Primary tumours:prostate (14%), breast (48%), lung (21%)
Interventions	8 Gy x 1 vs 4 Gy x 6
Outcomes	Overall response Re-treatment Fracture
Notes	Missing data in pain assessment: Not reported Side effects: Nausea and vomiting 77% vs 33% Diarrhoea 30% vs 22% Skin reaction 30% vs 22% Time point taken for pain response analysis in this review: Same as the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Foro 1998a

Methods	Randomized controlled trial Quality score (1/0/0) Pain assessment criteria: Visual analogue scale (VAS) Response - improvement by 2 or more points at any assessment Pain assessment schedule: one month then 3 monthly for 1 year or till death
Participants	Painful bone metastasis. Included at risk of pathological # or cord compression Randomised sites: 25 vs 25 vs 25 Primary tumours:prostate (15%), breast (40%), lung (17%)
Interventions	8 Gy x 1 vs 5 Gy x 3

Foro 1998a (*Continued*)

	vs 3 Gy x 10
Outcomes	Overall response
Notes	Missing data in pain assessment:13 / 75 (17.3%) Time point taken for pain response analysis in this review: Same as the study Side effects: Transient increase in pain in single dose arm 15%

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Foro 1998b

Methods	Randomized controlled trial
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Gaze 1997

Methods	Randomized controlled trial Quality score (1/0/0) Pain assessment criteria: 5 point categorical pain score and analgesic score Response - improvement of pain score by 1 category at 1 week or 1 month assessment Complete response - pain score = 0 Pain assessment schedule: 1 week, 1 month and then 2 monthly after treatment
Participants	Painful bone metastasis. Life expectancy < 4 weeks, cord compression, established or threatened pathological # excluded Randomised sites: 151 vs 144 Primary tumours:prostate (20%), breast (44%), lung (16%)

Gaze 1997 (*Continued*)

Interventions	10 Gy x 1 vs 4.5 Gy x 5
Outcomes	Overall response Complete response
Notes	Missing data in pain assessment:55 / 295 (18.6%) Time point taken for pain response analysis in this review: Same as the study Side effects: Grade 3/4 tiredness and latssitude 13% vs 16% Grade 3/4 nausea and vomiting 12% vs 15%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Kagei 1990

Methods	Randomized controlled trial Quality score (1/0/0) Pain assessment criteria: Four point categorical pain score Response - improvement of pain score by at least 1 category at 8-week assessment Complete response - pain score =0 Pain assessment schedule: 1,2,3,4 and 8 weeks after start of treatment
Participants	Painful metastasis Exclusion: fracture and spinal cord compression Randomised sites: 14 vs 13 Primary tumours:prostate (7%), breast (15%), lung (19%)
Interventions	8 or 10 or 12 or 15 Gy x 1 vs 5 Gy x 4 or 5 Gy x 5 or 5 Gy x 6
Outcomes	Overall response Complete response
Notes	Missing data in pain assessment:0/27 (0%) Time point taken for pain response analysis in this review: Same as the study Side effects: Nausea and vomiting 14% vs 23% Diarrhoea 21% vs 15% Transient increase in pain 0% vs 8%

Kagei 1990 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Koswig 1999

Methods	Randomized controlled trial Quality score (1/0/0) Pain assessment criteria: information N/A Pain assessment schedule: Day after, 6 weeks, 3 and 6 months after RT
Participants	Painful bone metastasis Randomised sites: 52 vs 55 Primary tumours:prostate (10%), breast (58%), lung (24%)
Interventions	8 Gy x 1 vs 3 Gy x 10
Outcomes	Overall response Complete response
Notes	Missing data in pain assessment: not reported Time point taken for pain response analysis in this review: Same as the study Side effects: not reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Nielsen 1998

Methods	Randomized controlled trial Quality score (1/1/1) Pain assessment criteria: Visual analogue scale and a 5 point categorical scale Response - > 50% reduction in VAS or improvement of at least one category at any time point Complete response - complete absence of pain Pain assessment schedule: 4, 8, 12, 20 weeks after beginning of RT
Participants	Painful bone metastases with life expectancy > 6 weeks Pathological # and cord compression excluded

Nielsen 1998 (*Continued*)

	Randomised sites: 122 vs 119 Primary tumours:prostate (33%), breast (39%), lung (12%)
Interventions	8 Gy x 1 vs 4 Gy x 5
Outcomes	Overall response Complete response Re-treatment Fracture
Notes	Missing data in pain assessment:32 / 239 (13.4%) Time point taken for pain response analysis in this review: Visual analogue scale at 4 weeks

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Ozsaran 2001a

Methods	Randomized controlled trial Quality score (1/0/0) Pain assessment criteria: 4 categorical scales for pain and analgesic requirement Response - Considerable pain relief, minimal analgesic requirement (60-90% response) Complete response - complete pain relief (100% response) Pain assessment schedule: 10 days, 1 month and 3 months after RT
Participants	Painful bone metastasis Randomised sites: 36 vs 38 vs 35 Primary tumours:prostate (5%), breast (44%), lung (26%)
Interventions	8 Gy x 1 vs 4 Gy x 5 vs 3 Gy x 10
Outcomes	Overall response
Notes	Missing data in pain assessment:Information N/A Time point taken for pain response analysis in this review: Pain response at 1 month

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Ozsaran 2001a (*Continued*)

Allocation concealment (selection bias)	Unclear risk	B - Unclear

Ozsaran 2001b

Methods	Randomized controlled trial
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Price 1986

Methods	Randomized controlled trial Quality score (1/0/0) Pain assessment criteria: 4 -point category for pain Response - improvement by at least 1 category within 1 year Complete response - no pain Pain assessment schedule: 2 weeks, 1,2,3,4,5,6,8,10 and 12 months
Participants	Painful bone metastases with life expectancy > 6 weeks Exclusion: pathological # of long bone Randomised sites: 140 vs 148 Primary tumours:prostate (8%), breast (37%), lung (20%)
Interventions	8 Gy x 1 vs 3 Gy x 10
Outcomes	Overall response Complete response Re-treatment Fracture Spinal cord compression
Notes	Missing data in pain assessment:At 4 weeks, 179 / 288 (62%) At 3 months, 199 / 288 (69%) Time point taken for pain response analysis in this review: At 4 weeks

Price 1986 (*Continued*)

	Side effects: no increase in acute toxicities	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Steenland 1999

Methods	Randomized controlled trial Quality score (1/0/1) Pain assessment criteria: 11-point category Response - decrease by at least 2 points within 1 year Complete response - pain score 0,1 independent of analgesic use Pain assessment schedule: Weekly for 3 months then 4 weekly up to 2 years	
Participants	Painful bone metastases with pain score > 2 Exclusion: pathological # or spinal cord compression Randomised sites: 579 vs 578 Primary tumours:prostate (23%), breast (39%), lung (25%)	
Interventions	8 Gy x 1 vs 4 Gy x 6	
Outcomes	Overall response Complete response Re-treatment Fracture Spinal cord compression	
Notes	Missing data in pain assessment:95 / 1157 (8%) Time point taken for pain response analysis in this review: Within 1 year Side effects: Nausea, vomiting and skin reaction same	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Warde 2001

Methods	Randomized controlled trial Quality score (1/0/0) Pain assessment criteria: Response - decrease in pain sore with reduced analgesics or pain score of zero without increase in analgesic at 3 months after treatment Pain assessment schedule: Information N/A
Participants	Painful bone metastasis with life expectancy > 4 months Randomised sites: 200 vs 198 Primary tumours:prostate (23%), breast (40%), lung (26%)
Interventions	8 Gy x 1 vs 4 Gy x 5
Outcomes	Overall response
Notes	Missing data in pain assessment:137 / 398 (34%) Time point taken for pain response analysis in this review: Same as the study Side effects: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Arcangeli 1998	Non-randomised study, mainly comparing different schedules of multifraction radiotherapy
Blitzer 1985	Randomised study comparing different schedules of multifraction radiotherapy
Borojevic 1999	Randomised study comparing different schedules of multifraction radiotherapy
Bremer 1999	Non-randomised study
Foro 1998	Randomised study comparing different schedules of single fraction radiotherapy
Hirokawa 1988	Randomised study comparing different schedules of multifraction radiotherapy
Hoskin 1992	Randomised study comparing different schedules of single fraction radiotherapy
Jeremic 1998	Randomised study comparing different schedules of single fraction radiotherapy

(*Continued*)

Madsen 1983	Randomised study comparing different schedules of multifraction radiotherapy
Maranzano 2000	Ongoing randomised study comparing different schedules of multifraction radiotherapy
Niewald 1996	Randomised study comparing different schedules of multifraction radiotherapy
Okawa 1988	Randomised study comparing different schedules of multifraction radiotherapy
Poulter 1992	Randomised study addressing the role of single dose half body irradiation on top of multifraction local field radiotherapy
Rasmusson 1995	Randomised study comparing different schedules of multifraction radiotherapy
Salazar 1996	Non-randomised study for pain caused by disseminated malignancy
Salazar 2001	Randomised study comparing different schedules of multifraction half-body irradiation
Tombolini 1994	Non-randomised study
Tong 1982	Same randomised study data as Blitzer 1985. Study comparing different schedules of multifraction radiotherapy
Zelefsky 1989	Non-randomised study

Characteristics of ongoing studies *[ordered by study ID]*

Roos 2000

Trial name or title	Trans-Tasman Radiation Oncology Group (TROG) 96.05
Methods	
Participants	Patients with bone metastasis causing neuropathic bone pain
Interventions	8 Gy x 1 vs 4 Gy x 5
Outcomes	Overall response 59% (response of each arm not reported)
Starting date	Feb 96
Contact information	
Notes	

DATA AND ANALYSES

Comparison 5. Intention-to-treat

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall response	13	3548	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.89, 1.19]
1.1 Overall pain response	13	3548	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.89, 1.19]
2 Complete response	7	2876	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.94, 1.30]
2.1 Complete pain response	7	2876	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.94, 1.30]
3 Re-treatment rate	5	2476	Odds Ratio (M-H, Fixed, 95% CI)	3.44 [2.67, 4.43]
4 Pathological fracture rate	5	2476	Odds Ratio (M-H, Fixed, 95% CI)	1.82 [1.06, 3.11]
5 Spinal 1	3	2206	Odds Ratio (M-H, Fixed, 95% CI)	1.41 [0.72, 2.75]
6 Spinal 2	3	739	Odds Ratio (M-H, Fixed, 95% CI)	1.43 [0.72, 2.83]

Comparison 6. Evaluable patients (i.e. excluding dropout patients)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall response	13	2966	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.76, 1.06]
1.1 All studies	13	2966	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.76, 1.06]
2 Complete response	7	2432	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.87, 1.22]
2.1 All studies	7	2432	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.87, 1.22]
3 Re-treatment	5	2369	Odds Ratio (M-H, Fixed, 95% CI)	3.49 [2.71, 4.50]
4 Pathological fracture	5	2394	Odds Ratio (M-H, Fixed, 95% CI)	1.81 [1.05, 3.11]
5 Spinal 1	3	2126	Odds Ratio (M-H, Fixed, 95% CI)	1.39 [0.71, 2.71]
6 Spinal 2	3	739	Odds Ratio (M-H, Fixed, 95% CI)	1.43 [0.72, 2.83]

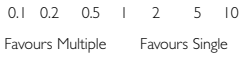
Analysis 5.1. Comparison 5 Intention-to-treat, Outcome 1 Overall response.

Review: Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy

Comparison: 5 Intention-to-treat

Outcome: 1 Overall response

Study or subgroup	Single fraction n/N	Multifraction n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Overall pain response					
BPTWP 1999	274/383	257/378		20.2 %	1.18 [0.87, 1.61]
Cole 1989	14/16	11/13		0.4 %	1.27 [0.15, 10.53]
Foro 1998a	19/25	21/25		1.4 %	0.60 [0.15, 2.47]
Foro 1998b	19/25	22/25		1.5 %	0.43 [0.09, 1.97]
Gaze 1997	108/151	99/144		7.9 %	1.14 [0.69, 1.88]
Kagei 1990	12/14	12/13		0.5 %	0.50 [0.04, 6.28]
Koswig 1999	41/52	45/55		2.5 %	0.83 [0.32, 2.15]
Nielsen 1998	52/122	56/119		8.9 %	0.84 [0.50, 1.39]
Ozsaran 2001a	27/36	28/38		1.9 %	1.07 [0.38, 3.04]
Ozsaran 2001b	27/36	29/35		2.0 %	0.62 [0.19, 1.98]
Price 1986	29/140	34/148		7.2 %	0.88 [0.50, 1.53]
Steenland 1999	392/579	361/578		32.1 %	1.26 [0.99, 1.61]
Warde 2001	45/200	63/198		13.5 %	0.62 [0.40, 0.97]
Total (95% CI)	**1779**	**1769**		**100.0 %**	**1.03 [0.89, 1.19]**
Total events: 1059 (Single fraction), 1038 (Multifraction)					
Heterogeneity: Chi^2 = 12.57, df = 12 (P = 0.40); I^2 =5%					
Test for overall effect: Z = 0.42 (P = 0.67)					
Test for subgroup differences: Not applicable					



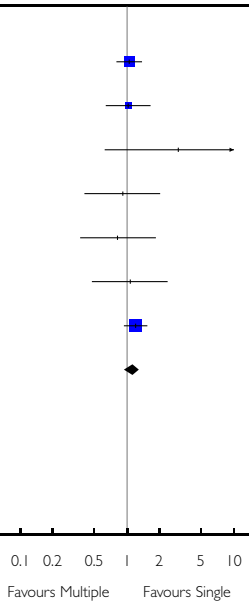
Analysis 5.2. Comparison 5 Intention-to-treat, Outcome 2 Complete response.

Review: Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy

Comparison: 5 Intention-to-treat

Outcome: 2 Complete response

Study or subgroup	Single fraction n/N	Multifraction n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Complete pain response					
BPTWP 1999	199/383	192/378		33.4 %	1.05 [0.79, 1.39]
Gaze 1997	50/151	47/144		11.6 %	1.02 [0.63, 1.66]
Kagei 1990	8/14	4/13		0.6 %	3.00 [0.62, 14.62]
Koswig 1999	16/52	18/55		4.4 %	0.91 [0.40, 2.06]
Nielsen 1998	12/122	14/119		4.6 %	0.82 [0.36, 1.85]
Price 1986	13/140	13/148		4.1 %	1.06 [0.47, 2.38]
Steenland 1999	199/579	175/578		41.3 %	1.21 [0.94, 1.54]
Total (95% CI)	**1441**	**1435**		**100.0 %**	**1.11 [0.94, 1.30]**
Total events: 497 (Single fraction), 463 (Multifraction)					
Heterogeneity: Chi^2 = 2.98, df = 6 (P = 0.81); I^2 =0.0%					
Test for overall effect: Z = 1.23 (P = 0.22)					
Test for subgroup differences: Not applicable					



Analysis 5.3. Comparison 5 Intention-to-treat, Outcome 3 Re-treatment rate.

Review: Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy

Comparison: 5 Intention-to-treat

Outcome: 3 Re-treatment rate

Study or subgroup	Single fraction n/N	Multifraction n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
BPTWP 1999	76/383	32/378		36.1 %	2.68 [1.72, 4.16]
Cole 1989	4/16	0/13		0.6 %	9.72 [0.47, 199.44]
Nielsen 1998	25/122	14/119		15.7 %	1.93 [0.95, 3.93]
Price 1986	15/140	4/148		4.9 %	4.32 [1.40, 13.36]
Steenland 1999	147/579	41/578		42.8 %	4.46 [3.08, 6.44]
Total (95% CI)	**1240**	**1236**		**100.0 %**	**3.44 [2.67, 4.43]**

Total events: 267 (Single fraction), 91 (Multifraction)

Heterogeneity: $Chi^2 = 6.28$, df = 4 (P = 0.18); $I^2 = 36\%$

Test for overall effect: Z = 9.58 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 5.4. Comparison 5 Intention-to-treat, Outcome 4 Pathological fracture rate.

Review: Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy

Comparison: 5 Intention-to-treat

Outcome: 4 Pathological fracture rate

Study or subgroup	Single fraction n/N	Multifraction n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
BPTWP 1999	7/383	2/378		9.7 %	3.50 [0.72, 16.96]
Cole 1989	0/16	1/13		7.8 %	0.25 [0.01, 6.74]
Nielsen 1998	6/122	6/119		28.3 %	0.97 [0.31, 3.11]
Price 1986	0/140	1/148		7.1 %	0.35 [0.01, 8.66]
Steenland 1999	24/579	10/578		47.0 %	2.46 [1.16, 5.18]
Total (95% CI)	**1240**	**1236**		**100.0 %**	**1.82 [1.06, 3.11]**

Total events: 37 (Single fraction), 20 (Multifraction)

Heterogeneity: $Chi^2 = 4.80$, df = 4 (P = 0.31); $I^2 = 17\%$

Test for overall effect: Z = 2.16 (P = 0.031)

Test for subgroup differences: Not applicable

Analysis 5.5. Comparison 5 Intention-to-treat, Outcome 5 Spinal 1.

Review: Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy

Comparison: 5 Intention-to-treat

Outcome: 5 Spinal 1

Study or subgroup	Single fraction n/N	Multifraction n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
BPTWP 1999	6/383	4/378		27.0 %	1.49 [0.42, 5.32]
Price 1986	2/140	1/148		6.5 %	2.13 [0.19, 23.76]
Steenland 1999	13/579	10/578		66.5 %	1.30 [0.57, 3.00]
Total (95% CI)	**1102**	**1104**		**100.0 %**	**1.41 [0.72, 2.75]**

Total events: 21 (Single fraction), 15 (Multifraction)

Heterogeneity: $Chi^2 = 0.15$, df = 2 (P = 0.93); $I^2 = 0.0\%$

Test for overall effect: Z = 1.00 (P = 0.32)

Test for subgroup differences: Not applicable

Analysis 5.6. Comparison 5 Intention-to-treat, Outcome 6 Spinal 2.

Review: Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy

Comparison: 5 Intention-to-treat

Outcome: 6 Spinal 2

Study or subgroup	Single fraction n/N	Multifraction n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
BPTWP 1999	6/129	4/123		27.9 %	1.45 [0.40, 5.27]
Price 1986	2/74	1/72		7.1 %	1.97 [0.17, 22.24]
Steenland 1999	13/168	10/173		65.0 %	1.37 [0.58, 3.21]
Total (95% CI)	**371**	**368**		**100.0 %**	**1.43 [0.72, 2.83]**

Total events: 21 (Single fraction), 15 (Multifraction)

Heterogeneity: $Chi^2 = 0.08$, df = 2 (P = 0.96); $I^2 = 0.0\%$

Test for overall effect: Z = 1.03 (P = 0.30)

Test for subgroup differences: Not applicable

Analysis 6.1. Comparison 6 Evaluable patients (i.e. excluding dropout patients), Outcome 1 Overall response.

Review: Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy

Comparison: 6 Evaluable patients (i.e. excluding dropout patients)

Outcome: 1 Overall response

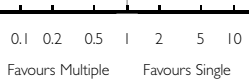
Study or subgroup	Single fraction n/N	Multifraction n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 All studies					
BPTWP 1999	274/351	257/330		19.4 %	1.01 [0.70, 1.45]
Cole 1989	14/16	11/13		0.5 %	1.27 [0.15, 10.53]
Foro 1998a	19/25	21/25		1.7 %	0.60 [0.15, 2.47]
Foro 1998b	19/25	22/25		1.8 %	0.43 [0.09, 1.97]
Gaze 1997	108/129	99/111		5.8 %	0.62 [0.29, 1.33]
Kagei 1990	12/14	12/13		0.6 %	0.50 [0.04, 6.28]
Koswig 1999	41/52	45/55		3.1 %	0.83 [0.32, 2.15]
Nielsen 1998	52/106	56/101		9.8 %	0.77 [0.45, 1.34]
Ozsaran 2001a	27/36	28/38		2.3 %	1.07 [0.38, 3.04]
Ozsaran 2001b	27/36	29/35		2.5 %	0.62 [0.19, 1.98]
Price 1986	29/43	34/45		3.6 %	0.67 [0.26, 1.70]
Steenland 1999	392/542	361/520		34.1 %	1.15 [0.88, 1.50]
Warde 2001	45/144	63/136		14.9 %	0.53 [0.32, 0.86]
Total (95% CI)	**1519**	**1447**		**100.0 %**	**0.90 [0.76, 1.06]**

Total events: 1059 (Single fraction), 1038 (Multifraction)

Heterogeneity: Chi^2 = 11.97, df = 12 (P = 0.45); I^2 =0.0%

Test for overall effect: Z = 1.31 (P = 0.19)

Test for subgroup differences: Not applicable



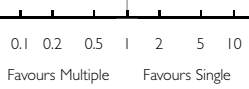
Analysis 6.2. Comparison 6 Evaluable patients (i.e. excluding dropout patients), Outcome 2 Complete response.

Review: Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy

Comparison: 6 Evaluable patients (i.e. excluding dropout patients)

Outcome: 2 Complete response

Study or subgroup	Single fraction n/N	Multifraction n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 All studies					
BPTWP 1999	199/351	192/330		32.2 %	0.94 [0.69, 1.28]
Gaze 1997	50/129	47/111		11.6 %	0.86 [0.51, 1.45]
Kagei 1990	8/14	4/13		0.7 %	3.00 [0.62, 14.62]
Koswig 1999	16/52	18/55		4.6 %	0.91 [0.40, 2.06]
Nielsen 1998	12/106	14/101		4.8 %	0.79 [0.35, 1.81]
Price 1986	13/49	13/48		3.6 %	0.97 [0.40, 2.39]
Steenland 1999	199/545	175/528		42.5 %	1.16 [0.90, 1.49]
Total (95% CI)	**1246**	**1186**		**100.0 %**	**1.03 [0.87, 1.22]**
Total events: 497 (Single fraction), 463 (Multifraction)					
Heterogeneity: Chi^2 = 3.89, df = 6 (P = 0.69); I^2 =0.0%					
Test for overall effect: Z = 0.36 (P = 0.72)					
Test for subgroup differences: Not applicable					



Analysis 6.3. Comparison 6 Evaluable patients (i.e. excluding dropout patients), Outcome 3 Re-treatment.

Review: Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy

Comparison: 6 Evaluable patients (i.e. excluding dropout patients)

Outcome: 3 Re-treatment

Study or subgroup	Single fraction n/N	Multifraction n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
BPTWP 1999	76/329	32/327		35.1 %	2.77 [1.77, 4.33]
Cole 1989	4/16	0/13		0.6 %	9.72 [0.47, 199.44]
Nielsen 1998	25/120	14/119		15.8 %	1.97 [0.97, 4.02]
Price 1986	15/140	4/148		4.9 %	4.32 [1.40, 13.36]
Steenland 1999	147/579	41/578		43.5 %	4.46 [3.08, 6.44]
Total (95% CI)	**1184**	**1185**		**100.0 %**	**3.49 [2.71, 4.50]**

Total events: 267 (Single fraction), 91 (Multifraction)

Heterogeneity: $Chi^2 = 5.78$, df = 4 (P = 0.22); $I^2 = 31\%$

Test for overall effect: Z = 9.66 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 6.4. Comparison 6 Evaluable patients (i.e. excluding dropout patients), Outcome 4 Pathological fracture.

Review: Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy

Comparison: 6 Evaluable patients (i.e. excluding dropout patients)

Outcome: 4 Pathological fracture

Study or subgroup	Single fraction n/N	Multifraction n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
BPTWP 1999	7/351	2/330		9.9 %	3.34 [0.69, 16.18]
Cole 1989	0/16	1/13		7.8 %	0.25 [0.01, 6.74]
Nielsen 1998	6/120	6/119		28.1 %	0.99 [0.31, 3.17]
Price 1986	0/140	1/148		7.1 %	0.35 [0.01, 8.66]
Steenland 1999	24/579	10/578		47.1 %	2.46 [1.16, 5.18]
Total (95% CI)	**1206**	**1188**		**100.0 %**	**1.81 [1.05, 3.11]**

Total events: 37 (Single fraction), 20 (Multifraction)

Heterogeneity: $Chi^2 = 4.64$, df = 4 (P = 0.33); $I^2 = 14\%$

Test for overall effect: Z = 2.15 (P = 0.032)

Test for subgroup differences: Not applicable

Analysis 6.5. Comparison 6 Evaluable patients (i.e. excluding dropout patients), Outcome 5 Spinal 1.

Review: Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy

Comparison: 6 Evaluable patients (i.e. excluding dropout patients)

Outcome: 5 Spinal 1

Study or subgroup	Single fraction n/N	Multifraction n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
BPTWP 1999	6/351	4/330		27.4 %	1.42 [0.40, 5.07]
Price 1986	2/140	1/148		6.5 %	2.13 [0.19, 23.76]
Steenland 1999	13/579	10/578		66.1 %	1.30 [0.57, 3.00]
Total (95% CI)	**1070**	**1056**		**100.0 %**	**1.39 [0.71, 2.71]**

Total events: 21 (Single fraction), 15 (Multifraction)

Heterogeneity: $Chi^2 = 0.14$, df = 2 (P = 0.93); $I^2 = 0.0\%$

Test for overall effect: Z = 0.96 (P = 0.34)

Test for subgroup differences: Not applicable

Analysis 6.6. Comparison 6 Evaluable patients (i.e. excluding dropout patients), Outcome 6 Spinal 2.

Review: Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy

Comparison: 6 Evaluable patients (i.e. excluding dropout patients)

Outcome: 6 Spinal 2

Study or subgroup	Single fraction n/N	Multifraction n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
BPTWP 1999	6/129	4/123		27.9 %	1.45 [0.40, 5.27]
Price 1986	2/74	1/72		7.1 %	1.97 [0.17, 22.24]
Steenland 1999	13/168	10/173		65.0 %	1.37 [0.58, 3.21]
Total (95% CI)	**371**	**368**		**100.0 %**	**1.43 [0.72, 2.83]**

Total events: 21 (Single fraction), 15 (Multifraction)

Heterogeneity: $Chi^2 = 0.08$, df = 2 (P = 0.96); $I^2 = 0.0\%$

Test for overall effect: Z = 1.03 (P = 0.30)

Test for subgroup differences: Not applicable

ADDITIONAL TABLES

Table 1. Re-analyses using evaluable patients only

	Single fraction	Multifraction	Odds ratio	P value	Heterogeneity
Overall pain response	70% (1059/1519)	71.7% (1038/1447)	0.90 (0.76-1.06)	0.19	0.45
Complete pain response	40% (497/1246)	39% (463/1186)	1.03 (0.87-1.22)	0.7	0.69
Re-treatment	22.6% (267/1184)	7.6% (91/1185)	3.49 (2.71- 4.5)	<0.00001	0.22
Fracture	3% (37/1206)	1.7% (20/1188)	1.81 (1.05-3.11)	0.03	0.33
Cord compression (all patients)	1.9% (21/1070)	1.4% (15/1056)	1.39 (0.71-2.71)	0.3	0.93

WHAT'S NEW

Date	Event	Description
5 April 2011	Amended	The primary author has indicated he will not be updating this review

HISTORY

Review first published: Issue 2, 2004

Date	Event	Description
28 May 2008	Amended	Converted to new review format.
15 September 2001	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Dr Wai Man Sze: Primary contact, literature search and screen, data extraction, analysis, draft manuscript, quality assessment.

Dr Mike Shelley: secondary contact, literature search, translations, review analysis, draft manuscript, quality assessment.

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DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital, Hong Kong.
- Velindre NHS Trust, Cardiff, UK.

External sources

- No sources of support supplied

NOTES

The primary author has indicated he will not be updating this review.

INDEX TERMS

Medical Subject Headings (MeSH)

Bone Neoplasms [*radiotherapy; *secondary]; Pain [etiology; *radiotherapy]; Palliative Care; Randomized Controlled Trials as Topic; Treatment Outcome

MeSH check words

Humans